JACC Vol. 27, No. 6
May 1996:1374–80

Repeated Coronary Artery Occlusions During Routine Balloon Angioplasty Do Not Induce Myocardial Preconditioning in Humans

PATRICK DUPOUY, MD, HERBERT GESCHWIND, MD, FACC, GABRIEL PELLE, PHD, EDUARDO APTECAR, MD, LUC HITTINGER, MD, AHMED EL GHALID, MD, JEAN-LUC DUBOIS-RANDÉ, MD, PHD

Créteil, France

Objectives. **The purpose of the present study was to assess whether brief, repeated coronary artery occlusions during balloon angioplasty induce a myocardial ischemic protective effect.**

Background. **In animals, brief coronary artery occlusions preceding a more prolonged occlusion result in reduced infarct size. Whether myocardial protection against ischemia could also occur in humans during angioplasty remains controversial.**

Methods. **Thirteen patients with a proximal left anterior descending coronary artery stenosis with no angiographic collateral circulation underwent percutaneous transluminal coronary artery balloon angioplasty. Three 120-s balloon inflations separated by a 5-min equilibration period were performed. For each inflation, intracoronary ST segment modifications, septal wall thickening (M-mode echocardiography), left ventricular pressures and time derivatives were measured at baseline and at 30, 60 and 90 s after balloon inflation and 120 s after balloon deflation.**

Results. **Intracoronary electrocardiographic analysis showed that the time course of the maximal ST segment elevation was identical at each inflation, as were wall motion changes assessed by the decrease in septal wall thickening. For the first and last inflations, peak positive dP/dt decreased significantly by 13 ± 9% (mean ± SD) and 14 ± 13%, whereas peak negative dP/dt increased by 23 ± 15% and 22 ± 10%, respectively (all $p < 0.01$ from baseline values). The relaxation time constant, tau, was altered similarly during the different inflations, from 44 ± 6 to 74 ± 13 ms and from 57 ± 13 to 77 ± 13 ms (all $p < 0.001$) for the first and last inflations, respectively. Left ventricular end-diastolic pressure increased to the same level after each inflation. In contrast to other hemodynamic variables, tau and left ventricular end-diastolic pressure did not return to baseline values in between the inflations, which may be due to myocardial stunning.**

Conclusions. **In patients with proximal left anterior descending coronary artery stenosis and no evidence of collateral circulation, brief periods of ischemia, such as those used during routine coronary balloon angioplasty, do not provide any protection against myocardial ischemia.**

(J Am Coll Cardiol 1996;27:1374–80)

Preconditioning and stunning are the major myocardial adaptative changes induced by a brief episode of reversible ischemia followed by arterial reperfusion. Ischemic preconditioning is a recent concept that was first detected in an experiment designed to deplete myocytes of adenosine triphosphate (ATP) using multiple, brief episodes of ischemia separated by periods of reperfusion (1). In this experiment, the final ATP content after four episodes of ischemia was no different from that found at the end of the first ischemic episode. Further experiments in dogs have shown that preconditioning can delay myocardial cell death. Indeed, myocardial preconditioning with four 5-min episodes of ischemia and reperfusion dramatically limited the size of infarctions caused by a subsequent 40-min episode of sustained ischemia (2). Consequently, definition of preconditioning was initially restricted to the decrease in myocardial cell death after previous short episodes of ischemia. This phenomenon has now been confirmed in other animal studies, which also show that brief coronary occlusions before more prolonged occlusions resulted not only in reduced infarct size but also in better recovery of systolic function (3–7). The shortest period of time required to precondition the myocardium is unclear and may differ in the different species. It seems, however, that preconditioning requires more than 30 s of ischemia but is fully developed after 5 min of ischemia has passed. In humans, it has been recently demonstrated that previous angina limits the infarct size or confers a beneficial effect on in-hospital outcome after acute myocardial infarction (8,9). Some workers proposed that myocardial protection in terms of pain, electrocardiographic (ECG) or contractility alterations induced by previous short episodes of ischemia may be related to a preconditioning effect (10). It has also been proposed that the preconditioning phenomenon should also occur in humans during standard percutaneous transluminal coronary angioplasty. Transient coronary artery occlusion during coronary angioplasty provides an excellent human model of myocardial ischemia, and recently it has been suggested that

From the Unité de Recherche U.400 de l'Institut National de la Santé et de la Recherche Médicale et Service des Explorations Fonctionnelles et Service de Cardiologie, Hôpital Henri Mondor, Créteil, France.

Manuscript received June 1, 1995; revised manuscript received December 31, 1995, accepted January 9, 1996.

Address for correspondence: Dr. Patrick Dupouy, Service des Explorations Fonctionnelles, Hôpital Henri Mondor, 51 Avenue du Maréchal De Lattre de Tassigny, 94010 Créteil, France.

0735-1097/96/$15.00
PII S0735-1097(96)00029-0

Table 1. Patient Characteristics at Baseline

Pt No.	Age (yr)/Gender	LVEF (%)	MBP (mm Hg)	HR (beats/min)	+dP/dt (mm Hg/s)	−dP/dt (mm Hg/s)	LVEDP (mm Hg)	Tau (ms)
1	65/F	70	116	68	2,300	−2,900	12	50
2	48/M	62	116	70	3,200	−2,500	5	38
3	55/F	59	110	58	2,800	−2,400	5	36
4	60/M	63	95	68	3,100	−2,410	10	33
5	50/M	64	90	75	2,380	−1,571	13	46
6	45/M	60	110	75	1,900	−2,600	12	47
7	59/F	75	115	72	1,700	−2,350	13	45
8	62/M	68	119	72	1,700	−2,300	2	38
9	50/M	65	105	70	2,400	−2,100	10	52
10	53/M	60	100	65	2,385	−2,250	8	47
11	65/M	60	110	70	3,000	−2,400	14	42
12	60/F	62	105	60	2,000	−2,050	5	54
13	58/M	60	95	75	2,590	−2,000	10	45
Mean ± SD	56 ± 7	64 ± 5	106 ± 9	69 ± 5	2,419 ± 506	−2,248 ± 318	9 ± 3.8	44 ± 6

dP/dt = first derivative of left ventricular pressure; F = female; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; M = male; MBP = mean blood pressure; Pt = patient.

successive brief coronary artery occlusions during angioplasty may decrease the clinical, ECG and hemodynamic alterations that occur at the first balloon inflation (10,11). Consequently, this myocardial protective action could modify the way we are actually performing angioplasty. A recent randomized study demonstrated the high clinical success of prolonged balloon inflations as compared with standard short dilations (12). In this context, interventional cardiologists would reduce the consequences of myocardial ischemia induced by angioplasty by preconditioning the myocardium before performing further prolonged balloon inflations. However, other investigators did not identify any myocardial protection after repeated episodes of ischemia (13,14), and in practice the protective myocardial effect of brief coronary artery occlusions remains controversial in humans. Differences between preconditioning studies may result from the different methods used to assess myocardial ischemia, which were limited to chest pain and ECG analysis.

Thus the present study was designed to assess the mechanistic consequences of brief, successive balloon occlusions throughout the cardiac cycle by analyzing intracoronary ECG, echocardiographic and hemodynamic changes in a selected group of patients with ischemia undergoing proximal left anterior descending coronary artery angioplasty.

Methods

Patients. The study included 13 patients (9 men, 4 women; mean [±SD] age 56 ± 7 years, range 48 to 65) selected from a group of patients scheduled for percutaneous transluminal coronary balloon angioplasty of proximal left anterior descending coronary artery stenosis. Baseline characteristics are listed in Table 1. To be included in this study, patients must have had evidence of anterior ischemia as documented by exercise stress test or thallium scintigraphy; one-vessel coronary artery disease with a mild coronary artery stenosis (>50% but <80% as assessed by quantitative coronary angiography) of the proximal left anterior descending coronary artery with no angiographic evidence of collateral filling of this artery (grade 0 according to the Rentrop classification); and normal wall motion assessed by both two-dimensional echocardiography and left ventriculography. Patients with unstable angina, recent or previous myocardial infarction, previous percutaneous transluminal coronary angioplasty procedure or clinical evidence of heart failure were excluded. No patient received a beta-adrenergic blocking agent within 72 h before the study. Calcium channel blocking agents and long-acting nitrate were stopped 48 h before angioplasty. Although the unrestricted use of short-acting sublingual nitroglycerin was allowed up to 1 h before the study, no patient required nitroglycerin before the procedure. Written informed consent was obtained from all patients before the study. Study protocol was approved by the local Ethical Committee.

Electrocardiographic study. Standard surface leads (I, III, aVF, V_3) were monitored. For eight patients intracoronary ECG was recorded on-line throughout the study using a 0.034 cm (0.014 in.) guide wire placed in the distal part of the dilated artery. These signals were recorded on paper at a speed of 25 mm/s just before and during all the inflations. Calibration was performed at the beginning of the procedure (1 mV = 10 mm). The ST segment elevation (mm) was measured 80 ms after the J point every 10 s from the beginning of the balloon inflation to 90 s.

Echocardiographic study. Septal M-mode images were obtained by a commercially available, phased-array system (CFM 750 Vingmed) with a 3.5-MHz transducer. Echocardiography was performed by M-mode imaging of the parasternal axis view just above the midpapillary muscle with a proximal depth focusing on the interventricular septum for measurement of the septal wall thickening. Gain settings were adjusted at the beginning of the protocol and were not changed thereafter. Septal wall thickness was then digitized with ECG and left ventricular pressure by a computer bit-pad connected to an

Apple Macintosh computer (Quadra 700). The mean value of three cardiac cycles was retained for analysis. End-diastolic wall thickness was measured at the onset of the Q wave. During ischemia, ischemic segments may contract after ejection is complete and including this contraction would produce erroneous results because it does not contribute to the mechanical pumping of the heart; therefore, we evaluated maximal systolic wall thickening at the point of maximal negative left ventricular dP/dt, as previously demonstrated (15). Echocardiographic measurements were performed by a different examiner from the one collecting the echocardiographic data.

Catheterization procedure. An 8F guiding catheter was positioned in the ostium of the left coronary artery using the Judkins technique. Nonionic contrast (Omnipaque, Nycomed, Oslo, Norway) was used to avoid a myocardial depressant effect during coronary opacification. Hemodynamic measurements were performed without contrast injection. A 5F microtip catheter transducer (Millar Industries) was placed into the left ventricle through the contralateral femoral artery to measure left ventricular systolic and end-diastolic pressures and derivatives (peak positive and negative dP/dt); aortic pressure was monitored through the guiding catheter.

The isovolumetric relaxation time constant (tau) was calculated using a mono exponential model: $P(t)=P_0e^{-t/T}$, where P is pressure, t is time and P_0 is the pressure at the time of peak negative dP/dt. P_0 and T parameters were estimated from a linear least-squares fit of $LnP = -t/T + LnP_0$ starting from the time of peak −dP/dt and ending when the pressure was 5 mm Hg above the minimal left ventricular diastolic pressure.

After placing the catheters, baseline hemodynamic measurements were obtained at the end of a 10-min equilibration period.

Study protocol. *Angioplasty procedure.* A total of three inflations were performed for each patient with a standard coronary angioplasty balloon catheter. The duration of each inflation was at least 120 s (mean 150 ± 20 s), separated by a 5-min period to allow for hemodynamic recovery. The mean balloon inflation pressure was 7 ± 2 atm. The mean balloon size was 2.8 ± 0.4 mm. At the beginning of each procedure 10,000 U of heparin was administered into a brachial vein. Dilatation was considered successful if a residual stenosis, assessed by quantitative coronary angiography, <50% was obtained.

Assessment of myocardial ischemia. Intracoronary and surface ECGs were monitored continuously throughout the study. Measurements of septal fractional shortening were made at the beginning of the procedure before and after placement of the guide wire through the lesion to precisely evaluate its potential ischemic action, then at 30, 60 and 90 s from the start of balloon inflation and finally 120 s after balloon deflation. Aortic blood pressure and left ventricular pressures and derivatives were measured immediately before each inflation and then at the same time as the echocardiographic measurements.

Statistical analysis. Results are expressed as mean value ± SD. Statistical significance was assumed when the null hypothesis could be rejected at the 0.05 probability level. The Student *t* test was used to compare paired and unpaired data. When serial changes in the hemodynamic variables were compared, repeated measures analysis of variance was used, followed by the Fisher protected least significant difference test or Dunnet's test for comparisons with baseline values.

Results

Intracoronary and surface ECG. Intracoronary ST segment elevation during balloon inflations is shown in Figure 1. For the first and third balloon inflations, the time course and the magnitude of ST segment elevation were identical from baseline to 90 s of ischemia. After balloon deflation for all patients, repolarization returned to normal within 40 ± 10 s. The time to reach the maximal shift of the ST segment was the same at each inflation, 38 ± 20 s, 42 ± 20 s and 35 ± 14 s for the first, second and third inflations, respectively (p = NS). Heart rate increased similarly during the three consecutive balloon coronary artery occlusions (Table 2).

On the surface ECG an upward shift of the ST segment was observed for all patients during the first balloon inflation. During the next two inflations, all but one patient had a similar ST segment elevation (1.8 ± 1.2 mV, 1.8 ± 1.4 mV and 1.35 ± 0.9 mV, respectively; p = NS). After balloon deflation repolarization returned to normal within 40 ± 10 s for all patients.

Septal wall thickening. At baseline, septal wall thickening was 45 ± 7%. Septal wall thickening was not affected by placing the guiding catheter or the guide wire through the proximal left anterior descending coronary artery stenosis. Each coronary occlusion induced a similar decrease in septal wall thickening (12 ± 5%, 14 ± 10% and 11 ± 6%; p = NS). Figures 1 and 2 show that the time course and the magnitude of the decrease in septal wall thickening were the same at the first and last inflations. In between inflations, septal wall thickening recovered to values obtained at baseline (p = NS).

Aortic pressure and left ventricular function. *Aortic pressure.* Mean aortic pressure decreased during each balloon inflation ($p < 0.05$). The magnitude of this decrease (between 3% and 5%) was similar for each ischemic period (Table 2).

Left ventricular end-diastolic pressure. Left ventricular end-diastolic pressure increased for each inflation to the same maximal value (Table 2). During the first balloon inflation, left ventricular end-diastolic pressure increased quickly within 30 s and reached a plateau of 29 ± 5 mm Hg after 1 min. After balloon deflation, left ventricular end-diastolic pressure decreased within 2 min but did not return to baseline values despite the 5-min equilibration period (Table 2). Left ventricular end-diastolic pressure changes exhibited a similar pattern during the second and third inflations, reaching a maximal value at 90 s (Table 2). After the third inflation, the pressure returned to 20 ± 7 mm Hg within 2 min after balloon deflation, which was also significantly different from the initial baseline values ($p < 0.01$).

Peak positive dP/dt. The maximal decrease in peak positive dP/dt was 14 ± 9% (p = 0.001), 11 ± 16% (p = 0.03) and 14 ± 13% (p = 0.01) for the first, second and third inflations,

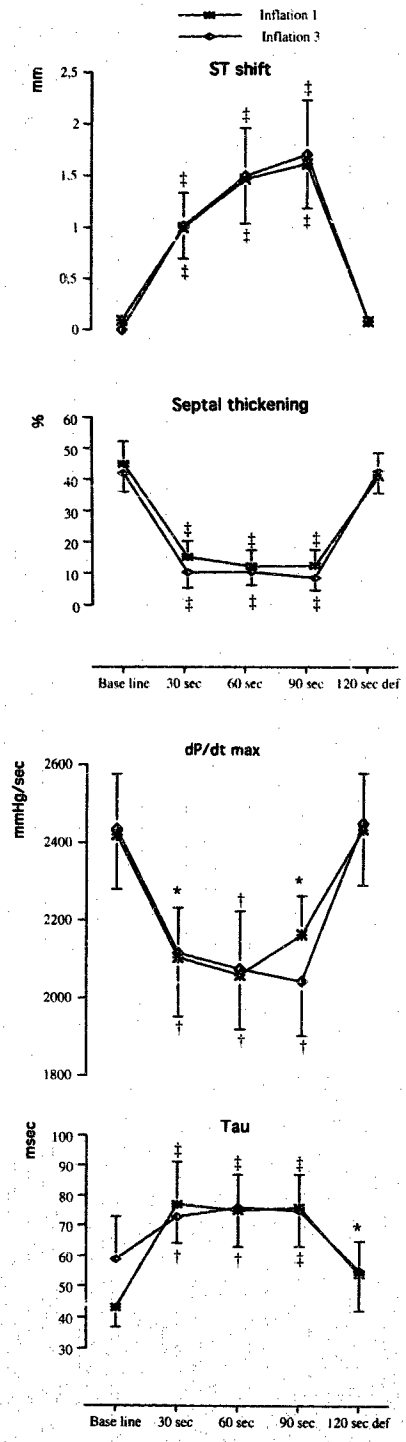

Figure 1. Intracoronary electrocardiographic, echocardiographic and hemodynamic changes evaluated at different times of ischemia and after balloon deflation (def) for the first and third balloon coronary artery occlusions. **Top panel,** Intracoronary ST segment elevation and echocardiographic septal wall thickening changes. **Bottom panel,** Peak positive left ventricular dP/dt and relaxation constant tau. For all variables there was a significant change from 30 s after the balloon inflation, which persisted throughout the ischemic episode. Changes were similar for the first and third inflations. Note that tau did not return to baseline values 120 s after the end of ischemia. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ versus corresponding baseline values.

respectively. Figure 1 shows that the decrease in peak positive dP/dt during ischemia was similar at the first and last inflations. The maximal decrease in peak dP/dt occurred within 90 s of the first and second inflations and within 60 s of the third inflation. These values equilibrated to those observed before balloon inflation within 2 min after balloon deflation (p = NS).

Peak negative dP/dt. Coronary artery occlusion increased peak negative dP/dt. For the first, second and third inflations, the maximal increase in peak negative dP/dt was 23 ± 15% ($p < 0.01$), 17 ± 16% ($p < 0.01$) and 22 ± 10% ($p < 0.01$), respectively. The magnitude of the increase was similar between the first and the last inflation. Values returned close to those observed before balloon inflation within 2 min after balloon deflation (Table 2).

Table 2. Values and Magnitude of Hemodynamic Changes During Each Balloon Inflation

	Baseline	Peak	% Change	p Value
Heart rate (beats/min)				
Inflation 1	69 ± 5	78 ± 9	13 ± 11	0.007
Inflation 2	67 ± 6	78 ± 6	17 ± 11	0.0006
Inflation 3	69 ± 9	79 ± 6	16 ± 11	0.001
MBP (mm Hg)				
Inflation 1	106 ± 9	104 ± 8	−3 ± 3	0.01
Inflation 2	109 ± 9	104 ± 6	−5.2 ± 5	0.006
Inflation 3	110 ± 8	105 ± 7	−3.4 ± 5	0.06
LVEDP (mm Hg)				
Inflation 1	9 ± 4	30 ± 4	336 ± 277	0.0001
Inflation 2	17 ± 9	29 ± 6	131 ± 183	0.009
Inflation 3	19.1 ± 7	32 ± 5.8	84 ± 59	0.0001
dP/dt max (mm Hg/s)				
Inflation 1	2,419 ± 506	2,059 ± 515	−13 ± 8.7	0.001
Inflation 2	2,434 ± 510	2,051 ± 394	−11.5 ± 15.7	0.03
Inflation 3	2,450 ± 508	2,036 ± 399	−14.3 ± 13.1	0.01
dP/dt min (mm Hg/s)				
Inflation 1	−2,248 ± 318	−1,750 ± 473	−23 ± 15	0.001
Inflation 2	−2,180 ± 454	−1,753 ± 412	−17 ± 16	0.002
Inflation 3	−2,163 ± 420	−1,688 ± 398	−22 ± 10	0.003
Tau (ms)				
Inflation 1	44 ± 6	74 ± 13	81 ± 42	0.0001
Inflation 2	52 ± 10	76 ± 12	44 ± 30	0.0005
Inflation 3	57 ± 13	77 ± 13	31 ± 29	0.009

Data presented are mean value ± SD. dP/dt = first derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; MBP = mean blood pressure.

JACC Vol. 27, No. 6
May 1996:1374–80

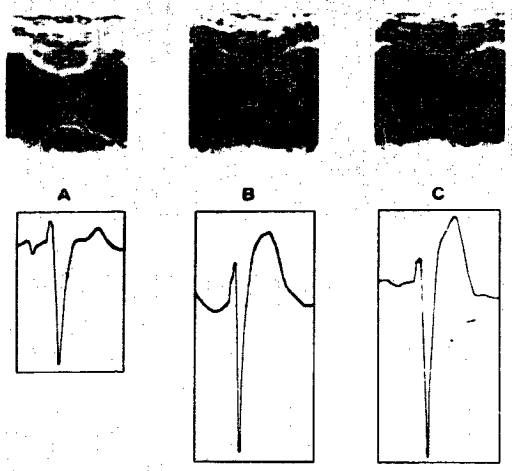

Figure 2. Effects of balloon coronary artery occlusions on septal wall thickening and intracoronary electrocardiogram. The ischemia induced by percutaneous transluminal coronary angioplasty of the proximal left anterior descending coronary artery similarly altered myocardial contractility, as demonstrated by the M-mode echocardiographic study during the first and third balloon inflations (**B, C**) as compared with baseline (**A**). The intracoronary electrocardiographic study shows a similar upward shift during the first and third balloon-induced ischemia episodes (**B, C**) as compared with baseline (**A**).

Relaxation time constant (tau). During the first balloon inflation tau increased from 44 ± 6 ms to 74 ± 13 ms ($p = 0.0001$), which was reached within 30 s of coronary artery occlusion and remained stable throughout the ischemic period (Fig. 1). After balloon deflation tau decreased to 52 ± 10 ms, which remained statistically different from baseline values ($p = 0.02$). Consequently, during the second period of ischemia the increase in tau was less in magnitude but reached a maximal level of 76 ± 12 ms. After balloon deflation, tau decreased to 57 ± 13 ms ($p = 0.01$ from baseline values). During the third balloon inflation tau increased from 57 ± 13 ms to 77 ± 13 ms at 30 s ($p = 0.009$) and had a parallel shift thereafter when compared with the first inflation (Fig. 1). After 120 s of deflation tau decreased to 55 ± 13 ms, higher than initial baseline values ($p < 0.01$).

Discussion

The present study shows that in patients with a single proximal left anterior descending coronary artery stenosis with no evidence of angiographic coronary collateral circulation, brief episodes of ischemia do not induce myocardial protection, as evidenced by intracoronary ECG, echocardiographic and hemodynamic alterations. These data do not provide evidence for myocardial preconditioning during standard coronary angioplasty.

Whether brief coronary artery occlusions may induce myocardial protection against further ischemic episodes remains controversial in humans (12). Recently, it was suggested that prodromal angina may reduce infarct size by preconditioning the myocardium (9). However, in this study, the duration of the ischemic periods needed to protect the myocardium against further prolonged ischemia might have been long and most of them probably silent. Coronary angioplasty provides an excellent human model to study the effects of ischemia. It has been extensively demonstrated that the monitoring of left ventricular hemodynamic status and echocardiography were accurate for assessing the consequences of ischemia on left ventricular function (13). Indeed, in humans, most studies aimed at evaluating myocardial protection focused mainly on the clinical (i.e., chest pain or ECG changes) but few assessed ECG, echocardiographic or invasive left ventricular hemodynamic changes together. Moreover, variables used to evaluate systolic and diastolic left ventricular function have never been used in the setting of preconditioning. In the present study, ECG, left ventricular hemodynamic and wall motion changes were examined, but chest pain was not considered because it is too subjective a variable. Additionally, the current study used a homogeneous selected group of patients with proximal left anterior descending coronary artery stenosis, normal left ventricular ejection fraction, no wall motion abnormalities and no collateral circulation.

Alteration in left ventricular performance during angioplasty. In the present study, hemodynamic changes occurring during ischemia were similar to those observed in previous studies (16). Indeed, transient occlusion of the proximal left anterior descending coronary artery induced myocardial contractility alterations, as evidenced by the decrease in both peak positive dP/dt and septal wall thickening. Additionally, it was associated with an alteration in left ventricular relaxation with an increase in peak negative dP/dt and with a prolongation of the isovolumetric relaxation time constant, tau (16). In this study, it is noteworthy that the left ventricular end-diastolic pressure and the isovolumic relaxation time constant remained abnormal in between balloon inflations. The explanation for these persistent alterations is complex. Abnormalities of relaxation observed during ischemia are due to combined mechanisms (modification of load, alteration of myocytes, inactivation and nonuniformity of relaxation) (17). Serruys et al. (16) extensively described the left ventricular performance during brief (40 to 60 s) balloon coronary artery occlusions. They showed an early onset of asynchronous relaxation with an early response in peak negative dP/dt and the time constant of relaxation. These changes were reversible. After four to six balloon inflations, regional wall motion abnormalities disappeared within 5 min after the completion of the angioplasty procedure, concomitant with the normalization of lactate metabolism (16). In the present study, despite differences of tau in between inflations, a similar prolongation of tau was reached after each inflation, which showed that no protective effect was evidenced on hemodynamic variables exploring both left ventricular contractility and relaxation.

In the present study, a persistent increase in end-diastolic pressure was observed after the first inflation. The shift of the

diastolic pressure during ischemia has been shown to be associated with an upward shift in the pressure–volume relation, which may be attributed to several factors (17,18). However, there is also evidence that diastolic function may be more sensitive to the consequence of ischemia than systolic function. Wijns et al. (19) reported that global and regional diastolic function was still abnormal 12 min after the end of the procedure in patients undergoing coronary angioplasty, as evidenced by a persistent increase in the constant of regional elastic stiffness. These observations suggest that myocardial stunning can develop in humans even after very mild ischemic insults and that diastolic function is affected to a greater extent than systolic function.

No evidence of preconditioning after brief coronary occlusion in humans. The time required to establish preconditioning in humans remains poorly known (2,20). In experimental studies, a single 5-min episode of ischemia has been shown to induce the preconditioned state in dogs (5) and in swine (21). Human studies during coronary artery bypass grafting also suggest that as little as 180 s of ischemia may induce preconditioning and consequently myocardial protection. In this study preconditioning was defined as the nondecrease of ATP level after repetitive brief episodes of ischemia (22). This short occlusion period allowing preconditioning supports the hypothesis that this phenomenon may also occur in humans, especially during standard coronary angioplasty where coronary occlusions of 90 to 120 s are common. Of the different mechanisms involved in the preconditioning phenomenon induced by brief ischemia, K_{ATP} channels and activation of alpha$_1$-adenosine receptors seem to play a major role (23,24). The main finding of the present study shows that there was no difference in the magnitude of intracoronary ECG, hemodynamic and echocardiographic changes at the second and third balloon inflations, as compared with the first one. These results agree with those previously reported by Feldman et al. (13) and Zalewski et al. (14), both of whom failed to demonstrate any alleviation of myocardial ischemia induced by successive balloon inflations. Additionally, Serruys et al. (16) did not observe any change in lactate production during sequential coronary artery occlusions.

In contrast, other investigators (10,11,24) found a decrease in chest pain and ST segment elevation after the first balloon inflation was completed. Deutsch et al. (10) showed a decrease in lactate production, suggesting a protective anti-ischemic effect of brief, repeated coronary artery occlusions in humans, which could mirror the preconditioning phenomenon found in experimental studies. However, the relation of the collateral circulation to ischemic effects of angioplasty is a crucial factor in human studies, potentially decreasing myocardial ischemia during coronary angioplasty. Cribier et al. (11) showed the heterogeneity of recruitable collateral branches in the setting of coronary angioplasty—a finding which may explain the apparent discrepancies observed between the different studies exploring myocardial protection of sequential brief coronary artery occlusions in patients. Furthermore, the lack of angiographic evidence of collateral branches does not mean absence of collateral circulation. In the present study we took care to evaluate not only patients with no angiographic collaterality but also patients without high grade stenosis, which is known to be accompanied by collateral circulation (25). This patient selection decreased the potential of important collateral recruitment during coronary angioplasty and avoided guide wire induced–myocardial ischemia, which may occur during angioplasty of very tight stenoses before beginning the procedure. Indeed, the protective effect reported (10,11) might be due to ischemia occurring before the first inflation as a consequence of partially occluding a coronary artery at the site of a tight stenosis. This effect did not occur in the present study, as demonstrated by the lack of echocardiographic wall motion changes after placing both the guiding catheter and the guide wire.

The method of analyzing the anti-ischemic effect of repetitive balloon coronary artery occlusion may influence the conclusions. Left ventricular pressure monitoring combined with echocardiographic analysis has been shown to be an accurate methodology for assessing the myocardial consequences of ischemia (26,27) but has never been clearly used in the field of preconditioning. In studies evaluating myocardial protection in patients with proximal left anterior descending coronary artery stenosis using hemodynamic measurements, no evidence of preconditioning was observed, similar to data in the present study (11,16). More likely, a stunned myocardial phenomenon was demonstrated by data reflecting impairment of the diastolic phase of the cardiac cycle. However, it is recognized that stunning is not the primary cause of the preconditioning phenomenon (28). It may be argued that the effect of repeated ischemia is additive (20) and that more inflations would have demonstrated some myocardial protective effect. This study was designed to assess the effect of repetitive ischemia under the conditions of a standard angioplasty procedure, which rarely uses more than three or four inflations of 120 s each.

Limitations of the study. In the present study, the evaluation of the collateral circulation was limited to the angiographic grades, which are known to underestimate the true collateral supply. Collateral branches were not assessed by transballoon pressure or flow measurements. However, very tight stenoses were excluded. It is unlikely that the collateral circulation significantly affected the results, because the development of a retrograde flow through the occluded artery would have protected the myocardium against ischemia. This phenomenon was not observed in the present study.

Maximal septal wall thickening as an index of ischemia may be misleading because of the asynchronous motion between normal and hypoxic muscle induced by regional acute myocardial ischemia (15). The present study focused on the same myocardial region during successive episodes of ischemia. Because of special efforts to ensure that the M-mode beam did not move throughout the study, the effect of each balloon inflation seemed to be reproducible. Moreover, paradoxical septal wall motion or postsystolic contraction during the periods of ischemia was not observed.

The patients included in this study had stable angina but may have had chronic myocardial ischemia with no possibility to demonstrate any protective action of brief, repeated coronary artery occlusions. However, because a relatively homogeneous patient group without high grade stenosis and without wall motion abnormalities was selected, it is unlikely that such a mechanism could have affected the results.

Clinical implications. In the traditional definition of preconditioning brief periods of ischemia are supposed to offer protection against a subsequent severe or lethal ischemic insult. This definition has progressively been extended to myocardial protection, but with no convincing demonstration of the reality of a preconditioning phenomenon. The possibility of preconditioning the myocardium could be of interest in the clinical arena. During angioplasty, preconditioning the myocardium by brief periods of ischemia would allow the infarct size to be limited in case of complications (dissection or thrombus), inducing a prolonged occlusion. This also would strengthen the usefulness of bypass surgery to obtain revascularization in case of irreversible, acute closure during angioplasty, especially if myocardial protection can be obtained by preconditioning. However, the present study failed to demonstrate that during a normal angioplasty procedure, brief inflations of 120 s induce myocardial protection in terms of ECG changes or contractility. This negative study raises concern about the reality of a preconditioning phenomenon during standard balloon angioplasty. Consequently, repeated short balloon inflations do not contribute to the management of coronary angioplasty with respect to decreasing the adverse effects of ischemia and allowing longer balloon inflations. The use of other myocardial ischemic protective means, such as perfusion balloon or anti-ischemic drugs, should be preferred to limit myocardial ischemia during routine coronary angioplasty.

References

1. Reimer KA, Murry CE, Yamasawa I. Four brief periods cause no cumulative ATP loss or necrosis. Am J Physiol 1986;251:H1306–H1315.
2. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124–36.
3. Iwamoto T, Miura T, Adachi T, et al. Myocardial infarct size-limiting effect of ischemic preconditioning was not attenuated by oxygen free-radical scavengers in the rabbit. Circulation 1991;83:1015–22.
4. Cohen MV, Liu GS, Downey JM. Preconditioning causes improved wall motion as well as smaller infarcts after transient coronary occlusion in rabbits. Circulation 1991;84:341–9.
5. Li GC, Vasquez JA, Gallagher KP, Lucchesi BR. Myocardial protection with preconditioning. Circulation 1990;82:609–19.
6. Liu GS, Thornton J, Van Winkle DM, Stanley AWH, Olsson RA, Downey JM. Protection against infarction afforded by preconditioning is mediated by alpha$_1$ adenosine receptors in rabbit heart. Circulation 1991;84:350–6.
7. Richard V, Kaeffer N, Tron C, Thuillez C. Ischemic preconditioning protects against coronary endothelial dysfunction induced by ischemia and reperfusion. Circulation 1994;89:1254–61.
8. Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? Circulation 1995;91:37–47.
9. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size. A role of ischemic preconditioning. Circulation 1995;91:291–7.
10. Deutsch E, Berger M, Kussmaul WG, Hirshfeld JW Jr, Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty. Clinical, hemodynamic, and metabolic features. Circulation 1990;82:2044–51.
11. Cribier A, Korsatz L, Koning R, et al. Improved myocardial ischemic response and enhanced collateral circulation with long repetitive coronary occlusion during angioplasty: a prospective study. J Am Coll Cardiol 1992;20:578–86.
12. Ohman EM, Marquis JF, Ricci DR, et al. A randomized comparison of the effects of gradual prolonged versus standard primary balloon inflation on early and late outcome: results of a multicenter clinical trial. Circulation 1994;89:1118–25.
13. Feldman RL, Macdonald RG, Hill J, Limacher MC, Conti R, Pepine CJ. Effect of propranolol on myocardial ischemia occurring during acute coronary occlusion. Circulation 1986;4:727–33.
14. Zalewski A, Goldberg S, Dervan JP, Slysh S, Maroko PR. Myocardial protection during transient coronary artery occlusion in man: beneficial effects of regional β-adrenergic blockade. Circulation 1986;73:734–9.
15. Smalling RW, Ekas RD, Felli PR, Binion L, Desmond J. Reciprocal functional interaction of adjacent myocardial segments during regional ischemia: an intraventricular loading phenomenon affecting apparent regional contractile function in the intact heart. J Am Coll Cardiol 1986;7:1335–6.
16. Serruys PW, Wijns W, van den Brand M, et al. Left ventricular performance, regional blood flow, wall motion, and lactate metabolism during transluminal angioplasty. Circulation 1984;1:25–36.
17. Gilbert JC, Glantz SA. Determinant of left ventricular filling and of the diastole pressure-volume relation. Circ Res 1989;64:827–52.
18. Grossman W, McLaurin LP. Diastolic properties of the left ventricle. Ann Intern Med 1976;84:316–26.
19. Wijns W, Serruys PW, Slager CJ, et al. Effect of coronary occlusion during percutaneous transluminal angioplasty in humans on left ventricular chamber stiffness and regional diastolic pressure-radius relations. J Am Coll Cardiol 1986;7:455–61.
20. Murry CE, Jennings RB, Reimer KA. New insights into potential mechanisms of ischemic preconditioning. Circulation 1991;84:442–5.
21. Schott RJ, Rohmann S, Braun ER, Schaper W. Ischemic preconditioning reduces infarct size in swine myocardium. Circ Res 1990;66:113–42.
22. Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. Lancet 1993;342:276–7.
23. Tomai F, Crea F, Gaspardone A, et al. Blockade of alpha$_1$-adenosine receptors prevents myocardial preconditioning in man [abstract]. Eur Heart J 1996;Suppl 15:553.
24. Tomai F, Crea F, Gaspardone A, et al. Ischemic preconditioning during coronary angioplasty is prevented by Glibenclamide, a selective ATP-sensitive K+ channel blocker. Circulation 1994;90:700–5.
25. Pieper JJ, Koolen JJ, Hoedemaker G, David GK, Visser CA, Dunning AJ. Severity of single-vessel coronary arterial stenosis and duration of angina as determinants of recruitable collateral vessels during balloon angioplasty occlusion. Am J Cardiol 1991;67:13–7.
26. Labovitz AJ, Lewen MK, Kern M, Vandormael M, Deligonal U, Kennedy HL. Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischemia produced by angioplasty. J Am Coll Cardiol 1987;10:748–55.
27. Kern MJ, Pearson A, Woodruff R, Deligonal U, Vandormael M, Labovitz A. Hemodynamic and echocardiographic assessment of the effects of diltiazem during transient occlusion of the left anterior descending coronary artery during percutaneous transluminal coronary angioplasty. Am J Cardiol 1989;64:849–55.
28. Jennings RB, Murry CE, Reimer KA. Energy metabolism in preconditioned and control myocardium. Effect of total ischemia. J Mol Cell Cardiol 1991;23:1449–58.